Remarks

Amendments to the Claims

Claim 1 is amended to specify that step (b) follows step (a). This amendment is supported throughout the specification, for example in Example 7. Minor clarifying amendments are made to claims 2 and 3. Claim 4 is amended to delete "liver," which now is recited in new claim 13. New claims 14-22 are supported by original claims 1-5. Pigs (new claims 18-22) are disclosed in the specification, *e.g.*, in paragraph [48]. Non-transgenic maternal cells (new claims 17 and 19) are disclosed, *e.g.*, in paragraph [53].

None of the amendments adds new matter.

Rejection of Claims 1, 2, 4, 5, 7, and 8 Under 35 U.S.C. § 102(e)

Claims 1, 2, 4, 5, 7, and 8 stand rejected under 35 U.S.C. § 102(e) as anticipated by Wu, U.S. Patent 6,995,299. Applicants respectfully traverse the rejection.

A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference. *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631 (Fed. Cir. 1987). The identical invention must be shown in as complete detail as is contained in the claimed invention. *Richardson v. Suzuki Motor Co.*, 868 F.2d 1226, 1236 (Fed. Cir. 1989). The elements must be arranged as required by the claim. *In re Bond*, 910 F.2d 831, 833, 15 U.S.P.Q.2d 1566, 1567 (Fed. Cir. 1990).

Independent claim 1 comprises two steps and is amended to recite that step (a) is carried out first. Step (a) recites selectively destroying native cells in a fetal tissue without substantially reducing the number of maternal cells of the same tissue. Step (b) recites implanting foreign

replacement cells in the fetal host. On pages 3 and 4 of the non-final Office Action mailed August 20, 2007, the Examiner cites Wu as teaching:

1. propagation of human hepatocytes in non-human animals which have chimeric livers comprising human hepatocytes (title and abstract);
2. that "[t]he animal comprising the human hepatocytes is preferably a fetus" (col. 5, line 5); and
3. host animals (*i.e.*, the animals with the chimeric livers) which are transgenic and carry a gene which is toxic to hepatocytes (col. 12, line 62 to col. 13, line 4).

With respect to item (3), Wu teaches destroying the host animal's hepatocytes using either a transgene encoding a toxic molecule or a toxic agent; however, neither of these embodiments meets the limitations of claim 1. When the host animal carries a transgene encoding a toxic molecule, Wu explicitly teaches that prenatal destruction of hepatocytes before colonization with human hepatocytes should be avoided:

> To avoid destroying the animal's liver prior to colonization with human hepatocytes, it is desirable to utilize a promoter that is not particularly active prenatally. Otherwise, such transgenic animals may die in utero.

Col. 13, lines 8-11. Wu also discloses using transgenic mouse hosts which contain a mouse urokinase gene driven by a mouse albumin enhancer/promoter; "[b]ecause albumin is not produced by the fetal liver . . . , animals survived in utero because urokinase was not produced. Col. 13, lines 19-34. Thus, Wu teaches that one should not use a transgene to "selectively destroy[ing] native cells in a tissue of a fetal non-human mammal host," as recited in claim 1.

Wu also teaches reduction of host liver cells by administering a drug which liver cells metabolize to a toxic agent. Wu generally teaches:

> [s]uch a drug may be administered subsequent to tolerization but prior to human hepatocyte transplant. Preferably, there is a delay between exposure to the drug and death of host animal hepatocytes, so that the animal can maintain liver function while transplanted hepatocytes proliferate to a point where they are present in sufficient numbers to supply the level of liver function required for viability.

Col. 14, lines 41-48. This teaching does not anticipate claim 1, which explicitly recites "destroying native cells in a tissue of a fetal non-human mammal host" (emphasis added). The only example in Wu of administering such a drug is administration of retrorsine given at birth and again two weeks later. Col. 14, lines 49-63. Administration of the drug postnatally does not anticipate step (a) of claim 1, which recites administration to a fetal non-human mammal host.

Wu does not teach each and every element of independent claim 1. Thus, Wu does not anticipate claim 1 or dependent claims 2, 4, 5, 7, and 8. Please withdraw the rejection.

Rejection of Claims Under 35 U.S.C. § 103(a)

The Final Office Action maintains the rejection of claims 1 and 3 as obvious over Wu in view of Loeb (U.S. Patent 6,451,571) and the rejection of claims 1 and 9-12 as obvious over Wu in view of Sorscher (U.S. Patent 6,017,896). Applicants respectfully traverse both rejections.

As discussed above, Wu does not teach each selectively destroying native cells in a fetal tissue without substantially reducing the number of maternal cells of the same tissue (claim 1, step a) and then implanting foreign replacement cells in the fetal host (claim 1, step b). Wu teaches inducing tolerance in an immunocompetent host non-human animal, preferably a fetus or a neonate (col. 5, lines 3-6), but Wu does not teach implanting foreign replacement cells in the fetus. Wu teaches introducing human hepatocytes for formation of a chimeric liver into the

tolerized animal (col. 5, lines 6-8), but Wu does not teach introducing the hepatocytes prenatally. The Patent and Trademark Office cannot pick and choose isolated elements of a reference and piece them together using Applicants' specification as a template:

> [s]tatements [in a prior art reference] cannot be viewed in the abstract. Rather, they must be considered in the context of the teaching of the entire reference. Further, a rejection cannot be predicated on the mere identification in [the reference] of individual components of claimed limitations. Rather, particular findings must be made as to the reason the skilled artisan, with no knowledge of the claimed invention, would have selected these components for combination in the manner claimed.

In re Kotzab, 217 F.3d 1365, 1371, 55 U.S.P.Q.2d 1313, 1317 (Fed. Cir. 2000). Such an exercise is improper because it uses hindsight rather than considering the art from the viewpoint of the ordinary artisan at the time the present application was filed. *Id.* at 1369, 55 U.S.P.Q.2d at 1316.

Wu does not teach or suggest the method of claim 1. As explained in the response filed December 16, 2007, neither Loeb nor Sorscher remedies the deficiencies of Wu. The Patent Office has therefore not made a *prima facie* case that independent claim 1 and dependent claims 3 and 9-12 are obvious because the cited references, even if combined, do not teach or suggest all the claim limitations.

Please withdraw the rejections.

Respectfully submitted,

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